CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA 21-310
Review number: 1
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Watson Laboratories Inc., Salt Lake City, UT

[redacted]

Reviewer: Karen Davis-Bruno
Division name: DMEDP
HFD #: 510
Review completion date: 5/11/01

Drug:

Trade name: Alora
Generic name: [redacted] estradiol [redacted]
transdermal delivery system
Code name: [redacted]
Chemical name: estra-1,3,5(10)-triene-3,17β-diol [redacted]

CAS registry number: 50-28-2 (estradiol) [redacted]
Molecular formula/molecular weight: $C_{18}H_{24}O_2$ MW=272.39 (estradiol), [redacted]

Relevant INDs/NDAs/DMFs: [redacted] NDA 20-655 (HFD-580) [redacted]

Drug class: [redacted] estrogen [redacted]

Indication: prevention [redacted] of postmenopausal osteoporosis

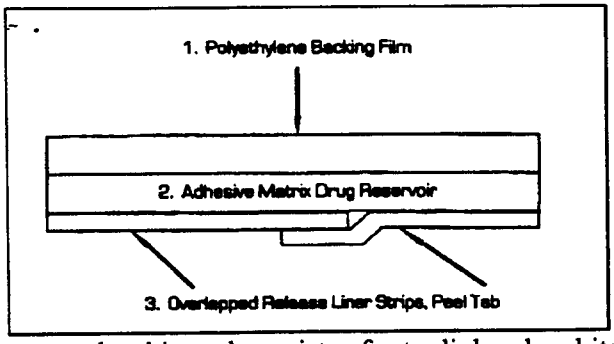
Clinical Dose: Three dosage strengths of Alora: 0.05, 0.075 and 0.1 mg/day are marketed with NDA 20-655 approved for treatment of moderate to severe vasomotor symptoms associated with menopause. A new dosage strength of 0.025 mg/day is being requested for the osteoporosis indication. The patch is applied every 3-4 days an alternate sides of the abdomen.

Clinical Experience: A 2 year multicenter, double blind, double dummy randomized placebo controlled parallel group study in 330 hysterectomized, non osteoporotic women with doses of 0.025, 0.05 and 0.075 mg/day Alora. All pateints received 1000 mg oral elemental calcium.

Drug Product:

Delivery Rate *in vivo*	Estradiol Content (mg)	Contact Surface (cm^2)
0.025	0.75	9
0.05	1.5	18
0.075	2.3	27
0.1	3	36

The Alora system consists of three layers from the polyethylene backing film, the adhesive



matrix drug reservoir contacts the skin and consists of estradiol and sorbitan monooleate dissolved in an acrylic adhesive. The polyester release liner protects the adhesive matrix during storage and is removed prior to use.

Route: **transdermal**

OVERALL SUMMARY AND EVALUATION: This NDA application is for an approved product at new lower dose for new osteoporosis indication, preclinical information has not been provided. NDA 20-655 was reviewed previously by DRUDP HFD-580 and is used to reference preclinical data. Pharmacology recommends approval with labeling changes indicated below.

Communication review:

Labeling review: Pregnancy Category X : [redacted] should not be used during pregnancy [redacted]

RECOMMENDATIONS:

External recommendations (to sponsor): Please revise the draft labeling for section F. Pregnancy Category as follows: Pregnancy Category X: [redacted] should not be used during pregnancy [redacted]

Reviewer signature: [redacted]

cc: HFD510/Davis-Bruno/

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/s/

Karen Davis-Bruno
5/14/01 11:49:28 AM
PHARMACOLOGIST

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